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SYNTHESIS OF ANALOGS OF NATURAL ISOFLAVONOIDS CONTAINING PHLOROGLUCINOL

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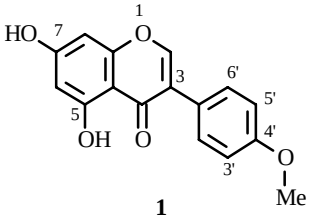
Analogs of the natural isoflavonoids biochanin A and orobol were synthesized. Alkylation involving phenolic hydroxyls and the chromone ring was studied.

Key words: Hesch synthesis, isoflavonoids, alkylation, aminomethylation.

Natural isoflavonoids occur as hydroxy-, methoxy-, methylenedioxy-, C-methyl-, and C-prenyl-derivatives. They can also be condensed with 2,2-dimethylpyrano- or furano-rings [1]. General syntheses of them and their natural distribution have been described [2].

Our goal was to synthesize and study the reactivity of analogs of the natural isoflavonoids biochanin A (**1**) and orobol (**2**).



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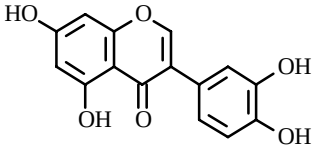

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Considering previous results [2], we used 2,4,6-trihydroxydeoxybenzoins **3a-c** to synthesize analogs of natural isoflavones. These are the most convenient starting materials for constructing the chromone system.

Starting ketones **3a-c** were prepared by condensation of phloroglucinol with substituted acetonitriles in ether in the presence of HCl and $ZnCl_2$ as a catalyst (Houben—Hoesch reaction) [3].

We used acylation of an α-methylene by Vilsmeier reagent in addition to acid (chloro)anhydrides to synthesize 2-(un)substituted analogs of **1** and **2**. Thus, the proposed [4] modified version that uses methanesulfonylchloride was successfully applied to the synthesis of isoflavonoids with "phloroglucinol" replacing the hydroxyls. Various isoflavonoids were synthesized by this method [5]. Use of this method with **3a-c** led to 2-unsubstituted isoflavonoids **4a-c**.

In contrast with the synthesis of 2-unsubstituted isoflavones, the use of traditional methods to construct the chromone ring is not always justified for isoflavones containing methoxys in ring B. Thus, use of acetic anhydride and triethylamine to synthesize 2-methylisoflavones **5a-c** did not lead to the desired compounds owing to low yields and difficulties with the isolation. Apparently in this instance the electron-donating groups in ring B of **3a-c** have an effect.

Therefore, we propose a different method for synthesizing 2-methylisoflavones **5a-c**. We used dimethylacetamide and methanesulfonylchloride in the presence of BF_3—etherate as the cyclization reagent. In contrast with the Kostanetskii—Robinson reaction, the use of this method produced 7-hydroxy-2-methylisoflavones **5a-c** in high yields in one step [6-8].

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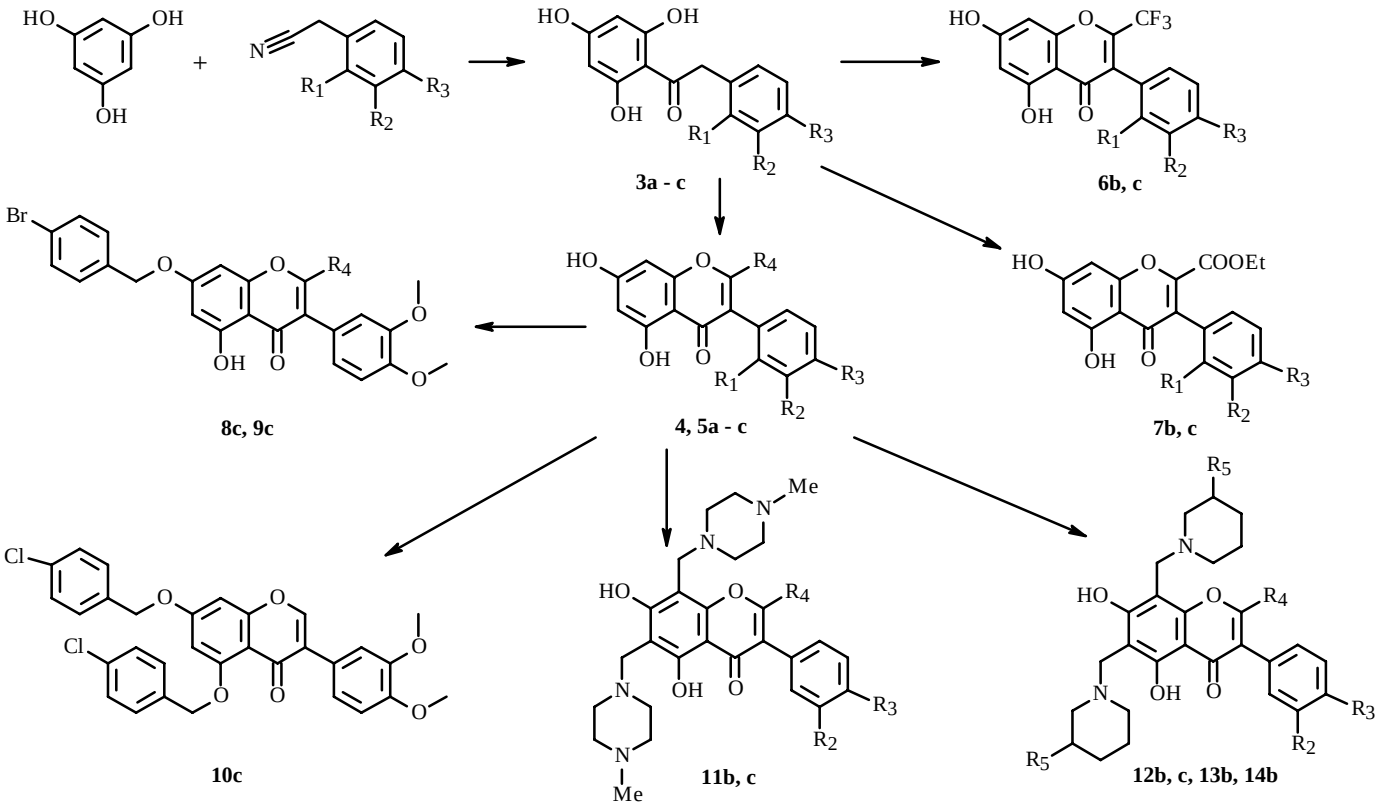

3 - 5a: R_1 = OMe, R_2 = R_3 = H; **3 - 7b**, **11**-**14b:** R_1 = R_2 = H, R_3 = OMe;
3 - 7c, **11c**, **12c:** R_1 = H, R_2 = R_3 = OMe; **4a - c**, **8c**, **11b**, **12b,c**, **14b:** R_4 = H;
5a - c, **9c**, **11c**, **13b**: R_4 = Me; **12b,c**, **13b**: R_5 = H; **14b:** R_5 = Me

2-Trifluoromethyl- and 2-ethoxycarbonyl isoflavones **6a-c** and **7a-c**, respectively, can be synthesized by using trifluoroacetic anhydride or ethoxyallylchloride [9].

We studied the alkylation of the prepared isoflavone analogs **4,5a-c**. Reaction with one equivalent of benzylhalide in acetone in the presence of potash produced 7-benzyloxy-5-hydroxyisoflavones **8c** and **9c**. Using an excess of the alkylating agent produced the *bis*-alkylated product **10c**.

We also studied the reactivity of isoflavones with substitution of hydroxyls by phloroglucinol in electrophilic-substitution reactions. The Mannich reaction was selected as an example. On one hand, Mannich bases are biologically active compounds with a wide spectrum of activity. On the other, they are promising starting compounds for further modification [10]. Introducing a tertiary nitrogen atom produces water-soluble salts for biological investigations. Furthermore, introducing an amine, analogously to previously described carboxyl [3, 11], makes it possible to test the products in immunological investigations since they can be incorporated into a polypeptide chain.

It should be noted that it is somewhat difficult to introduce an amine into the chromone fragment. Reactiton of 3-halochromones with primary or secondary amines does not always proceed smoothly. Sometimes a mixture of several products forms [12]. The synthesis of 5-aminoflavones is a multistep process [13].

Recalling the previous investigations of aminomethylation of benzopyrones [14], we prepared Mannich bases using aminals.

According to TLC, reaction of one equivalent of aminomethylating reagent forms a mixture of several products. Using an excess of *bis*(dialkylamino)methane led to aminomethylation of the 6- and 8-positions of the chromone ring to give **11-14b-c**.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates with elution by $CHCl_3$:MeOH mixtures (95:5 and 9:1). PMR spectra were measured on VXR-300 and Mercury 400 instruments (Varian, 300 and 400 MHz, respectively) in DMSO-d_6, except for Mannich bases **11-14b-c** ($CDCl_3$), relative to TMS (internal standard) on the δ scale. Elemental analyses corresponded to those calculated.

Starting ketones **3a-c** were prepared as before [3].

General Method for Preparing 4a-c. A solution of the appropriate **3a-c** (10 mmol) in DMF (10 mL) was treated with BF_3—etherate (40 mmol) and then methanesulfonylchloride (30 mmol) at a rate such that the temperature of the reaction mixture remained below 50°C. The mixture was held at 100°C and stirred for 3-4 h and then poured into cold water (100 mL). The resulting hydrolyzed precipitate of **4a-c** was filtered off and crystallized from MeOH.

5,7-Dihydroxy-3-(2-methoxyphenyl)chromen-4-one (4a), mp 200-201°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 3.74 (3H, s, OMe-2′), 6.24 (1H, d, H-6, $J_{6,8}$ = 2), 6.41 (1H, d, H-8, $J_{8,6}$ = 2), 6.98, 7.09, 7.25, 7.40 (4H, m, 3′,4′,5′,6′), 8.24 (1H, s, H-2), 10.92 (1H, s, OH-7), 12.86 (1H, s, OH-5).

General Method for Preparing 2-Methylisoflavones 5a-c. The synthesis was carried out analogously to that for **4a-c** using dimethylacetamide as the solvent and reagent. The reaction mixture was treated with methanesulfonylchloride and heated at 100°C with stirring for 16-24 h. The resulting crystals were filtered off and crystallized from MeOH.

5,7-Dihydroxy-3-(2-methoxyphenyl)-2-methylchromen-4-one (5a), mp 150-151°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 2.13 (3H, s, Me-2), 3.73 (3H, s, OMe-2′), 6.20 (1H, d, H-6, $J_{6,8}$ = 2), 6.36 (1H, d, H-8, $J_{8,6}$ = 2), 7.01, 7.10, 7.15, 7.39 (4H, m, 3′,4′,5′,6′), 10.83 (1H, s, OH-7), 12.91 (1H, s, OH-5).

5,7-Dihydroxy-3-(4-methoxyphenyl)-2-methylchromen-4-one (5b), mp 175-176°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 2.24, J/Hz (3H, s, Me-2), 3.80 (3H, s, OMe-4′), 6.20 (1H, d, H-6, $J_{6,8}$ = 2), 6.35 (1H, d, H-8, $J_{8,6}$ = 2), 6.99 (2H, d, $J_{3',2'}$ = 7, H-3, H-5), 7.22 (2H, d, $J_{2',3'}$ = 7, H-2, H-6), 10.87 (1H, s, OH-7), 12.95 (1H, s, OH-5).

3-(3,4-Dimethoxyphenyl)-5,7-dihydroxy-2-methylchromen-4-one (5c), mp 185-186°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 2.26 (3H, s, Me-2), 3.74, 3.79 (6H, 2s, OMe-3′, OMe-4′), 6.19 (1H, d, $J_{6,8}$ = 2, H-6), 6.36 (1H, d, H-8, $J_{8,6}$ = 2), 6.81 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 6.88 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.02 (1H, d, $J_{5',6'}$ = 8, H-5′), 10.80 (1H, s, OH-7), 12.97 (1H, s, OH-5).

General Method for Preparing 6,7a-c. A cooled solution of **3a-c** (10 mmol) in the minimal amount of pyridine was treated with ethoxyallylchloride (40 mmol) or trifluoroacetic anhydride. The reaction mixture was held at 0°C for 2 h, left at room temperature for 48-72 h, and poured into water (100 mL). The resulting precipitate was filtered off and crystallized from MeOH.

5,7-Dihydroxy-3-(4-methoxyphenyl)-2-trifluoromethylchromen-4-one (6b), mp 215-216°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 3.80 (3H, s, OMe-4′), 6.31 (1H, d, H-6, $J_{6,8}$ = 2), 6.49 (1H, d, H-8, $J_{8,6}$ = 2), 7.02 (2H, d, $J_{3',2'}$ = 2, H-3, H-5), 7.22 (2H, d, $J_{2',3'}$ = 7, H-7, H-6), 11.24 (1H, s, OH-7), 12.25 (1H, s, OH-5).

3-(3,4-Dimethoxyphenyl)-5,7-dihydroxy-2-trifluoromethylchromen-4-one (6c), mp 243-244°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 3.72, 3.80, J/Hz (6H, 2s, OMe-3′, OMe-4′), 6.31 (1H, d, H-6, $J_{6,8}$ = 2), 6.47 (1H, d, H-8, $J_{8,6}$ = 2), 6.83 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 6.93 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.01 (1H, d, $J_{5',6'}$ = 8, H-5′), 11.23 (1H, s, OH-7), 12.26 (1H, s, OH-5).

Ethyl 3-(3,4-dimethoxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-2-carboxylate (7c), mp 230-231°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 0.97, 4.12 (3H, t, 2H, q, J = 7, CH_3CH_2OOC-2), 3.72, 3.79 (6H, 2s, OMe-3′, OMe-4′), 6.28 (1H, d, H-6, $J_{6,8}$ = 2), 6.42 (1H, d, H-8, $J_{8,6}$ = 2), 6.80 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 6.89 (1H, d, $J_{2',6'}$ = 2, H-2′), 6.98 (1H, d, $J_{5',6'}$ = 8, H-5′), 11.13 (1H, s, OH-7), 12.52 (1H, s, OH-5).

7-(4-Bromobenzyloxy)-5-hydroxyisoflavones 8c and 9c. A hot solution of the appropriate **4c** or **5c** (10 mmol) in absolute acetone (15 mL) was treated with freshly calcined K_2CO_3 (2.1 g, 15 mmol), stirred and heated to 50-56°C, treated with 4-bromobenzylbromide (10.5 mmol), left for 4 h (completion of the reaction monitored by TLC), cooled, and poured onto acidified icewater (100 mL). The precipitate was filtered off and crystallized from MeOH.

7-(4-Bromobenzyloxy)-3-(3,4-dimethoxyphenyl)-5-hydroxychromen-4-one (8c), mp 171-172°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 3.79 (6H, s, OMe-3′, OMe-4′), 5.23 (2H, s, OCH_2-7), 6.50 (1H, d, H-6, $J_{6,8}$ = 2), 6.76 (1H, d, H-8, $J_{8,6}$ = 2), 7.03 (1H, d, $J_{5',6'}$ = 8, H-5′), 7.12 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 7.18 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.45, 7.61 (4H, 2d, $J_{2,3}$ = 8, benzyl protons), 8.49 (1H, s, H-2), 12.95 (1H, s, OH-5).

7-(4-Bromobenzyloxy)-3-(3,4-dimethoxyphenyl)-5-hydroxy-2-methylchromen-4-one (9c), mp 169-170°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 2.28 (3H, s, Me-2), 3.74, 3.79 (6H, 2s, OMe-3′, OMe-4′), 5.23 (2H, s, OCH_2-7), 6.47 (1H, d, H-6, $J_{6,8}$ = 2), 6.70 (1H, d, H-8, $J_{8,6}$ = 2), 6.83 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 6.90 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.00 (1H, d, $J_{5',6'}$ = 8, H-5′), 7.44, 7.61 (4H, 2d, $J_{2,3}$ = 8, benzyl protons), 12.98 (1H, s, OH-5).

5,7-*Bis*-(4-chlorobenzyloxy)-3-(3,4-dimethoxyphenyl)chromen-4-one (10c) was synthesized analogously to **8c** and **9c** using 4-chlorobenzylchloride (25 mmol). mp 182-183°C (MeOH). PMR spectrum (δ, ppm., J/Hz): 3.77 (6H, s, OMe-3′, OMe-4′), 5.23 (4H, 2s, OCH_2-7, OCH_2-5), 6.71 (1H, d, H-6, $J_{6,8}$ = 2), 6.80 (1H, d, H-8, $J_{8,6}$ = 2), 7.00 (1H, d, $J_{5',6'}$ = 8, H-5′), 7.05 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 7.10 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.50, 7.61 (6H, 2H, 2m, benzyl protons), 8.23 (1H, s, H-2).

General Method for Preparing 6,8-*Bis*(dialkylamino)methylisoflavones 11-14. A boiling solution of the appropriate isoflavone **4,5a-c** (10 mmol) in absolute dioxane (20 mL) was treated with aminal (25 mmol), boiled for 3-4 h (completion of the reaction monitored by TLC), and cooled. The dioxane, released amine, and unreacted aminal were evaporated in vacuum. The solid was crystallized from toluene—hexane.

5,7-Dihydroxy-3-(4-methoxyphenyl)-6,8-*bis*-(4-methylpiperazin-1-ylmethyl)chromen-4-one (11b), mp 183-184°C. PMR spectrum (δ, ppm., J/Hz): 2.29 (6H, s, 2N–Me), 2.35-2.80 (16H, m, piperazine protons), 3.79 (2H, s, N–CH_2), 3.84 (5H, s, N–CH_2 and OMe-4′), 6.99 (2H, d, $J_{3',2'}$ = 8, H-3, H-5), 7.44 (2H, d, $J_{2',3'}$ = 8, H-2, H-6), 7.87 (1H, s, H-2).

3-(3,4-Dimethoxyphenyl)-5,7-dihydroxy-2-methyl-6,8-*bis*-(4-methylpiperazin-1-ylmethyl)chromen-4-one (11c), mp 165-166°C. PMR spectrum (δ, ppm., J/Hz): 2.30 (9H, s, 2N–Me and Me-2), 2.35-2.80 (16H, m, piperazine protons), 3.80, 3.83 (4H, 2s, 2N–CH_2), 3.88, 3.91 (6H, 2s, OMe-3′ and OMe-4′), 6.78 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 6.83 (1H, d, $J_{2',6'}$ = 2, H-2′), 6.93 (1H, d, $J_{5',6'}$ = 8, H-5′).

5,7-Dihydroxy-3-(4-methoxyphenyl)-6,8-*bis*-piperidin-1-ylmethyl-chromen-4-one (12b), mp 139-140°C. PMR spectrum (δ, ppm., J/Hz): 1.27-1.82 and 2.34-2.83 (12H, m, 8H, m, piperidine protons), 3.73, 3.80 (4H, 2s, 2N–CH_2), 3.84 (3H, s, OMe-4′), 6.99 (2H, d, $J_{3',2'}$ = 8, H-3, H-5), 7.45 (2H, d, $J_{2',3'}$ = 8, H-2, H-6), 7.88 (1H, s, H-2).

3-(3,4-Dimethoxyphenyl)-5,7-dihydroxy-6,8-*bis*-piperidin-1-ylmethyl-chromen-4-one (12c), mp 137-138°C. PMR spectrum (δ, ppm., J/Hz): 1.30-1.74 and 2.36-2.79 (12H, m, 8H, m, piperdine protons), 3.73, 3.80 (4H, 2s, 2N–CH_2), 3.92, 3.93 (6H, 2s, OMe-3′ and OMe-4′), 6.93 (1H, d, $J_{5',6'}$ = 8, H-5′), 7.04 (1H, dd, $J_{6',2'}$ = 2, $J_{6',5'}$ = 8, H-6′), 7.10 (1H, d, $J_{2',6'}$ = 2, H-2′), 7.90 (1H, s, H-2).

5,7-Dihydroxy-3-(4-methoxyphenyl)-2-methyl-6,8-*bis*-piperdin-1-ylmethyl-chromen-4-one (13b), mp 113-114°C. PMR spectrum (δ, ppm., J/Hz): 1.32-1.78 and 2.39-2.75 (12H, m, 8H, m, piperidine protons), 2.29 (3H, s, Me-2), 3.75, 3.78 (4H, 2s, 2N–CH_2), 3.84 (3H, s, OMe-4′), 6.99 (2H, d, $J_{3',2'}$ = 8, H-3, H-5), 7.19 (2H, d, $J_{2',3'}$ = 8, H-2, H-6).

5,7-Dihydroxy-3-(4-methoxyphenyl)-6,8-*bis*-(3-methylpiperdin-1-ylmethyl)chromen-4-one (14b), mp 142-143°C. PMR spectrum (δ, ppm., J/Hz): 0.86 (6H, 2Me), 1.47-2.22 and 2.83-3.04 (14H, m, 4H, m, piperdine protons), 3.74, 3.80 (4H, 2s, 2N–CH_2), 3.84 (3H, s, OMe-4′), 6.99 (2H, d, $J_{3',2'}$ = 8, H-3, H-5), 7.44 (2H, d, $J_{2',3'}$ = 8, H-2, H-6), 7.87 (1H, s, H-2).

REFERENCES

1. P. M. Dewich, in: *The Flavonoids: Advances in Research*, J. B. Harborne and T. J. Mabry, eds., Chapman and Hall, London and New York (1982).
2. A. L. Kazakov, V. P. Khilya, V. V. Mezheretskii, and D. Litkei, *Natural and Modified Isoflavonoids* [in Russian], Izd. Rostov St. Univ., Rostov-on-Don (1985).
3. A. Pelter, R. S. Ward, and J. L. Whalley, *Synthesis-Stuttgart*, **12**, 1793 (1998).
4. R. J. Bass, *J. Chem. Soc. Chem. Commun.*, No. 2, 78 (1976).
5. S. Sepulveda-Boza, G. H. Walizei, et al., *Synth. Commun.*, **31**, No. 12, 1993 (2001).
6. A. C. Jain and P. K. Tuli, *Indian J. Chem., Sect. B*, **16**, No. 12, 1124 (1978).
7. A. C. Jain, D. K. Tuli, and R. Khazanchi, *Indian J. Chem., Sect. B*, **17**, No. 2, 123 (1979).
8. A. Pelter and S. Foot, *Synthesis*, No. 5, 326 (1976).
9. V. Szabo, S. Borbely, and M. Darbai, *Magy. Kem. Foly.*, **81**, No. 7, 311 (1975).
10. M. Tramontini, *Synthesis*, No. 12, 703 (1973).
11. N. Al-Maharik, I. Mutikainen, and K. Wahala, *Synthesis-Stuttgart*, No. 3, 411 (2000).

12. Y. Sugita, T. Iwaki, M. Okamoto, and I. Yokoe, *Heterocycles*, **55**, No. 5, 881 (2001).
13. T. Akama, H. Ishida, U. Kimura, K. Gomi, and H. Saito, *J. Med. Chem.*, **41**, 2056 (1998).
14. M. S. Frasinyuk, A. V. Turov, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 1072 (1998).